Journal of the American College of Cardiology Vol. 50, No. 12, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.06.015

Impact of Vessel Size on Outcome After Implantation of Sirolimus-Eluting and Paclitaxel-Eluting Stents

A Subgroup Analysis of the SIRTAX Trial

Mario Togni, MD,* Stéphanie Eber, BA,* Jeannette Widmer, BA,* Michael Billinger, MD,* Peter Wenaweser, MD,* Stéphane Cook, MD,* Rolf Vogel, MD, PhD,* Christian Seiler, MD, FACC,* Franz R. Eberli, MD,‡ Willibald Maier, MD,‡ Roberto Corti, MD,‡ Marco Roffi, MD,‡ Thomas F. Lüscher, MD,‡ Ali Garachemani, MD,* Otto M. Hess, MD, FACC,* Simon Wandel, MS,† Bernhard Meier, MD, FACC,* Peter Jüni, MD,† Stephan Windecker, MD*

Bern and Zurich, Switzerland

Objectives We assessed the impact of vessel size on angiographic and long-term clinical outcome after percutaneous coronary intervention (PCI) with sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) within a randomized trial (SIRTAX [Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization]).

Background Percutaneous coronary intervention in small-vessel disease is associated with an increased risk of major adverse cardiac events (MACE).

Methods A total of 1,012 patients were randomly assigned to treatment with SES (n = 503) or PES (n = 509). A stratified analysis of angiographic and clinical outcome was performed up to 2 years after PCI according to size of the treated vessel (reference vessel diameter ≤2.75 vs. >2.75 mm).

Results Of 1,012 patients, 370 patients (37%) with 495 lesions underwent stent implantation in small vessels only, 504 patients (50%) with 613 lesions in large vessels only, and 138 patients (14%) with 301 lesions in both small and large vessels (mixed). In patients with small-vessel stents, SES reduced MACE by 55% (10.4% vs. 21.4%; p = 0.004), mainly driven by a 69% reduction of target lesion revascularization (TLR) (6.0% vs. 17.7%; p = 0.001) compared with PES at 2 years. In patients with large- and mixed-vessel stents, rates of MACE (large: 10.4% vs. 13.1%; p = 0.33; mixed: 16.7% vs. 18.0%; p = 0.83) and TLR (large: 6.9% vs. 8.6%; p = 0.47; mixed: 16.7% vs. 15.4%; p = 0.86) were similar for SES and PES. There were no significant differences with respect to death and myocardial infarction between the 3 groups.

Conclusions Compared with PES, SES more effectively reduced MACE and TLR in small-vessel disease. Differences between SES and PES appear less pronounced in patients with large- and mixed-vessel disease. (The SIRTAX trial; http://clinicaltrials.gov/ct/show/NCT00297661?order=1; NCT00297661). (J Am Coll Cardiol 2007;50:1123–31)

Atherosclerosis of small coronary arteries remains a major challenge to revascularization procedures, because coronary artery bypass grafting is limited by high rates of technical failure (1), and percutaneous coronary interventions (PCI) are associated with an increased risk of restenosis and adverse outcome (2). Stent implantation results in arterial injury, initiating a vasculoproliferative cascade with smooth muscle cell proliferation and migration resulting in neointimal hyperplasia. The amount of neointimal hyperplasia is largely independent of vessel size and thus late luminal loss, an angiographic measure of neointimal hyperplasia, is similar across a wide range of vessel diameters (3,4). Accordingly, small vessels are more prone to restenosis than larger vessels, because they are less able to accommodate neointimal tissue without compromising blood flow (5).

From the Departments of *Cardiology and †Social and Preventive Medicine, University Hospital Bern, Switzerland; and the ‡Department of Cardiology, University Hospital Zurich, Zurich, Switzerland.

Manuscript received January 22, 2007; revised manuscript received June 7, 2007, accepted June 25, 2007.

JACC Vol. 50, No. 12, 2007
September 18, 2007:1123–31

Abbreviations and Acronyms

DES = drug-eluting stent(s)
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RVD = reference vessel diameter
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Results of randomized trials and observational studies comparing bare-metal stents with balloon angioplasty revealed conflicting results and only modest superiority of bare-metal stents in patients with small-vessel disease (6–9). Drug-eluting stents (DES) with site-specific delivery of therapeutic agents reduce neointimal hyperplasia more effectively and have been shown to improve clinical and angiographic measures of restenosis compared with bare-metal stents (10–12). In direct head-to-head comparisons, sirolimus-eluting stents (SES) consistently showed lower late luminal loss compared with paclitaxel-eluting stents (PES) (13,14). Although late luminal loss has been proposed as a robust marker for discriminating DES (15), its impact on clinical outcomes, such as target lesion revascularization (TLR), remains controversial, particularly in the low range of late loss typical for DES.

The SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) trial was a randomized controlled trial directly comparing the safety and efficacy of SES and PES in an "all comers" population undergoing PCI (14). In the overall population, SES provided lower late luminal loss, which translated into lower rates of clinical and angiographic restenosis. The objective of the present analysis was to evaluate the long-term clinical outcome based on an extended follow-up of 2 years and angiographic result of patients stratified according to vessel size, with the hypothesis that differences in outcome should be particularly pronounced in patients with small-vessel as opposed to large-vessel disease.

Methods

Study population. The SIRTAX trial was a prospective observer-blind randomized controlled study comparing safety and efficacy of SES and PES in 1,012 patients undergoing PCI (14). Eligible patients had a history of stable angina or acute coronary syndrome and presented with at least 1 lesion with a diameter stenosis ≥50% in a vessel with a reference vessel diameter (RVD) between 2.25 and 4.00 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels or on lesion length. Prespecified exclusion criteria were known allergy to aspirin, thienopyridines, stainless steel, sirolimus, paclitaxel, or contrast agents; participation in another coronary device study; and terminal illness. The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the institutional ethics committees at the University Hospitals of Bern and Zurich, Switzerland. All patients provided written informed consent. There was no industry involvement in design, conduct, or analysis of the study.

Randomization and coronary stent procedure. Randomization was concealed using sealed, opaque, and sequentially numbered envelopes. The allocation schedule was based on computer-generated random numbers, stratified according to trial center, and blocked, with block lengths of 6 and 10 varied randomly. Patients were randomly assigned on a 1:1 basis to treatment with SES (Cypher, Cordis, Miami Lakes, Florida), or PES (Taxus, Boston Scientific, Natick, Massachusetts). The SES were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 33 mm. The PES were

Table 1 Baseline Clinical Characteristics

	Small Vessels Only		Large Vessels Only		Small and Large Vessels		
	SES	PES	SES	PES	SES	PES	p Value*
Patients, n	183	187	260	244	60	78	
Age ≥65 yrs, n (%)	83 (45.4)	94 (50.3)	104 (40.0)	102 (41.8)	30 (50.0)	29 (37.2)	0.12
Males, n (%)	132 (72.1)	145 (77.5)	210 (80.8)	190 (77.9)	40 (66.7)	64 (82.1)	0.25
Diabetes mellitus, n (%)	37 (20.2)	35 (18.7)	51 (19.6)	43 (17.6)	20 (33.3)	15 (19.2)	0.21
Hypertension, n (%)	113 (61.8)	127 (67.9)	145 (55.8)	144 (59.0)	44 (73.3)	49 (62.8)	0.02
Hyperlipidemia, n (%)	119 (65.0)	107 (57.2)	152 (58.5)	142 (58.2)	34 (56.7)	43 (55.1)	0.51
Current smoking, n (%)	67 (36.6)	65 (34.8)	97 (37.3)	88 (36.1)	20 (33.3)	28 (35.9)	0.90
Previous MI, n (%)	57 (31.2)	62 (33.2)	71 (27.3)	65 (26.6)	17 (28.3)	25 (32.1)	0.24
Stable angina pectoris, n (%)	105 (57.4)	94 (50.3)	111 (42.7)	111 (45.5)	30 (50.0)	41 (52.6)	0.01
Acute coronary syndromes, n (%)	78 (42.6)	93 (49.7)	149 (57.3)	133 (54.5)	30 (50.0)	37 (47.4)	0.002
Unstable angina, n (%)	16 (8.7)	12 (6.4)	10 (3.9)	13 (5.3)	2 (3.3)	5 (6.4)	
Non–ST-segment elevation MI, n (%)	34 (18.6)	45 (24.1)	61 (23.5)	59 (24.2)	17 (28.3)	19 (24.4)	
ST-segment elevation MI, n (%)	28 (15.3)	36 (19.3)	78 (30.0)	61 (25.0)	11 (18.3)	13 (16.7)	
Multivessel disease, n (%)	120 (65.6)	111 (59.4)	130 (50.0)	125 (51.2)	50 (83.3)	66 (84.6)	<0.001

*The p values relate to differences between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both small and large vessels.

MI = myocardial infarction; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Table 2 Baseline Characteristics of Lesions

	Small Vessels Only		Large Vessels Only		Small and Large Vessels		
	SES	PES	SES	PES	SES	PES	p Value*
Lesions, n	249	246	314	299	131	170	
Target lesion coronary artery, n (%)							<0.001
Left main	2 (0.8)	2 (0.8)	7 (2.2)	7 (2.3)	2 (1.5)	2 (1.2)	
Left anterior descending	137 (55.0)	130 (52.9)	125 (39.8)	120 (40.1)	62 (47.3)	73 (42.9)	
Left circumflex	77 (30.9)	65 (26.4)	37 (11.8)	41 (13.7)	25 (19.1)	33 (19.4)	
Right	32 (12.9)	45 (18.3)	135 (43.0)	125 (41.8)	42 (32.1)	59 (34.7)	
Bypass graft	1 (0.4)	4 (1.6)	10 (3.2)	6 (2.0)	0 (0.0)	3 (1.8)	
ACC/AHA lesion class, n (%)							0.11
A	57 (22.9)	47 (19.1)	53 (16.9)	64 (21.4)	21 (16.0)	43 (25.3)	
B1	98 (39.4)	90 (36.6)	139 (44.3)	147 (49.2)	63 (48.1)	70 (41.2)	
B2	65 (26.1)	65 (26.4)	77 (24.5)	62 (20.7)	32 (24.4)	31 (18.2)	
C	29 (11.7)	44 (17.9)	45 (14.3)	26 (8.7)	15 (11.5)	26 (15.3)	
Angiographic measurements							
Lesion length (mm ± SD)	11.67 ± 6.40	11.97 ± 7.18	11.93 ± 7.06	12.61 ± 7.14	12.07 ± 8.05	12.62 ± 7.21	0.56
Reference vessel diameter (mm ± SD)	2.46 ± 0.20	2.46 ± 0.23	3.13 ± 0.26	3.16 ± 0.29	2.78 ± 0.36	2.75 ± 0.40	<0.001
Minimal lumen diameter (mm ± SD)	0.46 ± 0.35	0.43 ± 0.33	0.55 ± 0.51	0.60 ± 0.48	0.59 ± 0.45	0.57 ± 0.42	<0.001
Stenosis (% lumen diameter ± SD)	81.51 ± 13.76	82.54 ± 13.53	82.55 ± 15.95	81.29 ± 14.80	79.15 ± 15.33	79.13 ± 14.67	0.01

*The p values relate to differences between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both, small and large vessels.

ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Table 1.

available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 32 mm. All interventions were performed according to current practice guidelines for PCI. No mixture of DES was allowed within a given patient. After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months.

Study end points and definitions. Adverse events were assessed in the hospital, at 1, 6, and 9 months, and at 1 and 2 years. An independent clinical events committee unaware of the patients' treatment assignments adjudicated all end points. Patients were asked to return for angiographic follow-up study at 8 months.

Table 3 Procedural Results

	Small Vessels Only		Large Vessels Only		Small and Large Vessels		p Value for Interaction*
	SES	PES	SES	PES	SES	PES	
Lesions, n	249	246	314	299	131	170	
Procedures							
Lesions treated per patient (n ± SD)	1.4 ± 0.6	1.3 ± 0.6	1.2 ± 0.5	1.2 ± 0.5	2.2 ± 0.4	2.2 ± 0.4	0.65
Stents per lesion (n ± SD)	1.1 ± 0.4	1.2 ± 0.5	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.71
Minimal stent diameter (mm ± SD)	2.6 ± 0.2	2.6 ± 0.2	3.1 ± 0.3	3.1 ± 0.3	2.8 ± 0.3	2.8 ± 0.4	0.35
Stent length per lesion (mm ± SD)	18.0 ± 8.5	20.3 ± 11.9	19.4 ± 11.6	18.5 ± 10.4	18.3 ± 10.1	17.6 ± 8.9	0.03
Maximal pressure (atm ± SD)	13.9 ± 3.1	13.5 ± 2.8	14.9 ± 3.3	14.6 ± 3.0	14.0 ± 2.8	13.8 ± 2.6	0.89
Angiographic results							
Final minimal lumen diameter (mm ± SD)							
In-stent	2.36 ± 0.21	2.41 ± 0.22	2.91 ± 0.30	2.93 ± 0.34	2.60 ± 0.31	2.61 ± 0.36	0.67
In-segment	2.26 ± 0.27	2.31 ± 0.27	2.82 ± 0.34	2.93 ± 0.32	2.51 ± 0.37	2.50 ± 0.44	0.16
Final stenosis (% of lumen diameter ± SD)							
In-stent	6.64 ± 4.48	5.81 ± 4.19	7.69 ± 4.81	7.21 ± 6.44	7.54 ± 4.99	7.48 ± 5.17	0.61
In-segment	8.87 ± 7.06	7.82 ± 6.63	8.54 ± 7.02	8.13 ± 5.75	9.89 ± 8.74	9.54 ± 7.51	0.83
Acute gain (mm ± SD)							
In-stent	1.89 ± 0.36	1.98 ± 0.38	2.35 ± 0.54	2.34 ± 0.54	2.01 ± 0.49	2.04 ± 0.50	0.22
In-segment	1.79 ± 0.40	1.88 ± 0.42	2.34 ± 0.49	2.34 ± 0.57	1.95 ± 0.53	1.97 ± 0.54	0.51

Values are mean ± standard deviation. *The p values for interaction relate to differences between the 3 groups of patients in terms of differences in procedural results between SES and PES. Abbreviations as in Table 1.

JACC Vol. 50, No. 12, 2007
September 18, 2007:1123–31

Table 4 Clinical Events Through 2 Years

	Small Vessels Only				Large Vessels Only				Small and Large Vessels				
	SES	PES	Hazard Ratio (95% CI)	p Value*	SES	PES	Hazard Ratio (95% CI)	p Value*	SES	PES	Hazard Ratio (95% CI)	p Value*	p Value for Interaction*
Patients	183	187			260	244			60	78			
Death	11 (6.0)	10 (5.4)	1.10 (0.47 to 2.60)	0.82	14 (5.4)	14 (5.7)	0.93 (0.44 to 1.96)	0.85	0 (0.0)	3 (3.9)	0.19 (0.06 to 22.86)	0.13	0.96
Cardiac death	5 (2.7)	8 (4.3)	0.63 (0.21 to 1.92)	0.41	8 (3.1)	7 (2.9)	1.07 (0.39 to 2.95)	0.90	0 (0.0)	2 (5.6)	0.26 (0.06 to 26.50)	0.21	0.97
MI	7 (3.8)	7 (3.7)	1.01 (0.35 to 2.88)	0.99	9 (3.5)	14 (5.7)	0.60 (0.26 to 1.38)	0.23	2 (3.3)	3 (3.9)	0.86 (0.14 to 5.13)	0.87	0.73
TLR	11 (6.0)	33 (17.7)	0.31 (0.16 to 0.62)	0.001	18 (6.9)	21 (8.6)	0.79 (0.42 to 1.49)	0.47	10 (16.7)	12 (15.4)	1.08 (0.47 to 2.50)	0.86	0.04
Percutaneous	10 (5.5)	30 (16.0)	0.32 (0.15 to 0.64)	0.002	17 (6.5)	16 (6.6)	0.98 (0.50 to 1.95)	0.96	8 (13.3)	12 (15.4)	0.86 (0.35 to 2.11)	0.75	0.05
Surgical	1 (0.6)	5 (2.7)	0.20 (0.02 to 1.69)	0.14	2 (0.8)	7 (2.9)	0.39 (0.10 to 1.52)	0.18	2 (3.3)	2 (2.6)	1.90 (0.32 to 11.39)	0.48	0.20
TVR	14 (7.7)	36 (19.3)	0.38 (0.20 to 0.70)	0.002	22 (8.5)	24 (9.8)	0.85 (0.48 to 1.52)	0.59	11 (18.3)	14 (18.0)	1.04 (0.47 to 2.29)	0.92	0.07
Percutaneous	13 (7.1)	33 (17.7)	0.37 (0.20 to 0.71)	0.003	21 (8.1)	19 (7.8)	1.02 (0.55 to 1.90)	0.95	9 (15.0)	14 (18.0)	0.83 (0.36 to 1.93)	0.67	0.06
Surgical	1 (0.6)	5 (2.7)	0.20 (0.02 to 1.69)	0.14	2 (0.8)	7 (2.9)	0.39 (0.10 to 1.52)	0.18	2 (3.3)	2 (2.6)	1.90 (0.32 to 11.39)	0.48	0.20
Stent thrombosis	4 (2.2)	5 (2.7)	0.81 (0.22 to 3.01)	0.75	5 (1.9)	8 (3.3)	0.58 (0.19 to 1.78)	0.35	3 (5.0)	1 (1.3)	3.93 (0.41 to 37.80)	0.24	0.28
MACE	19 (10.4)	40 (21.4)	0.45 (0.26 to 0.78)	0.004	27 (10.4)	32 (13.1)	0.78 (0.46 to 1.29)	0.33	10 (16.7)	14 (18.0)	0.91 (0.41 to 2.05)	0.83	0.24
TVF	20 (10.9)	43 (23.0)	0.44 (0.26 to 0.75)	0.003	31 (11.9)	35 (14.3)	0.81(0.50 to 1.32)	0.40	11 (18.3)	16 (20.5)	0.88 (0.41 to 1.89)	0.74	0.18

Values are n (%). *The p values relate to differences between patients treated with SES as opposed to PES for each stratum. The p values for interaction relate to differences in hazard ratios between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both small and large vessels. Hazard ratios and p values are from Cox proportional hazards models.
CI = confidence interval; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization; other abbreviations as in Table 1.

The prespecified primary end point was a composite of major adverse cardiac events (MACE) up to 9 months, defined as cardiac death, myocardial infarction, or ischemia-driven revascularization of the target lesion (TLR). Secondary end points included ischemia-driven TLR, target vessel revascularization, or target vessel failure. The latter two were considered to be driven by ischemia if the stenosis of the target lesion or vessel was ≥50% on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms or if there was a stenosis of ≥70% in the absence of ischemic signs or symptoms. Target lesion revascularization was defined as a repeated revascularization based on a stenosis within the stent or within the 5-mm borders proximal or distal to the stent. The diagnosis of periprocedural myocardial infarction was established whenever new Q waves of at least 0.4 seconds' duration in at least 2 contiguous leads appeared on the electrocardiogram with an elevated creatine kinase-MB fraction level or, in the absence of pathologic Q waves, by an elevation in creatine kinase levels to more than twice the upper limit of normal with an elevated creatine kinase-MB or troponin I level. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either target vessel occlusion or thrombus within or adjacent to the previously successfully stented segment.

Quantitative coronary angiography. Coronary angiograms were digitally recorded at baseline, immediately after stent implantation, and at follow-up and were assessed at the angiographic core laboratory of the University Hospital Bern. Angiogram readers were unaware of the type of stent implanted. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). The intraobserver and interobserver reliabilities of the quantitative measurements have been reported previously (16).

Quantitative measurements included the RVD, the minimal luminal diameter, percentage diameter stenosis, and late luminal loss. Binary restenosis was defined as stenosis ≥50% in the target lesion at angiographic follow-up. All angiographic measurements of the target lesion were obtained in the stent and the areas within 5 mm proximal and distal to the stent edge.

Statistical analysis. A stratified analysis of clinical and angiographic outcomes, which was specified after completion of patient recruitment, was performed according to vessel size. We used quantitative coronary angiography to determine the RVD. Patients, who underwent stent implantation only in lesions with an RVD ≤2.75 mm were categorized as having undergone treatment of small vessels. Conversely, patients who underwent stent implantation only in lesions with an RVD >2.75 mm were categorized as having undergone treatment of large vessels. Patients with stent implantations in both small and large vessels were classified as "mixed." All randomized patients were included in the analysis of primary and secondary clinical outcomes in the groups to which they were originally allocated to

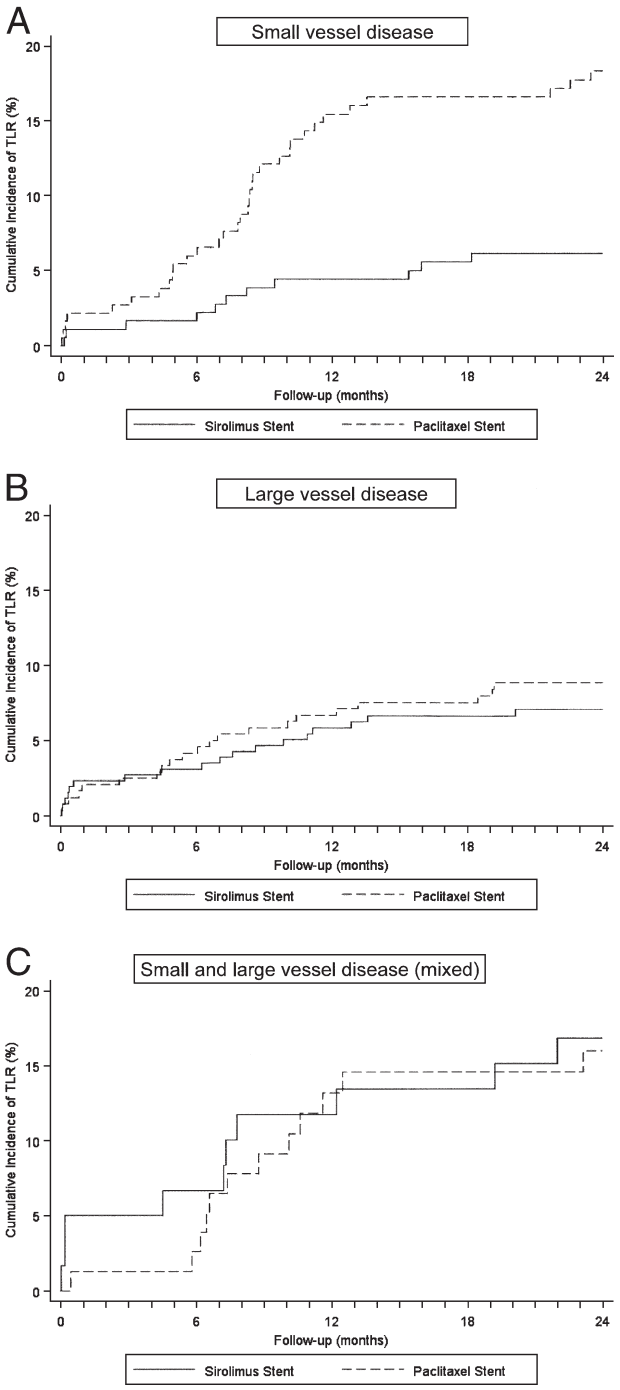

Figure 1 **Kaplan-Meier Cumulative Event Curves of TLR Stratified for Stent Type**

(A) Small vessels only; **(B)** large vessels only; **(C)** both small and large vessels (mixed). TLR = target lesion revascularization.

(intention-to-treat principle). Analyses of outcomes of the angiographic substudy were restricted to lesions from patients who attended follow-up angiography. We used a Cox proportional hazards model to compare clinical outcomes between the groups. To determine whether there was an interaction between treatment effect and type of vessel disease, we used likelihood ratio tests. Stratified analyses require about 4 times as many events to detect treatment by patient interactions of a magnitude of the overall treatment effect (17). The trial was designed to detect a relative risk of 0.5 of MACE in the primary analysis of all patients at 9 months, when 86 events had occurred, with a power of 90% (14). A post hoc power analysis based on 142 MACE that had occurred at up to 2 years indicated that the trial would have a power of 44% to detect an interaction between treatment and vessel size of a similar magnitude.

The differences in treatment effects between small- and large-vessel disease were driven by percutaneous TLR. For this end point we performed an additional series of sensitivity analyses: in addition to the term for the treatment by vessel size interaction, we included terms for interactions between treatment and age, gender, diabetes, hypertension, and acute coronary syndrome and determined whether the treatment by vessel size interaction was affected by the inclusion of these additional interaction terms. Analyses were performed in Stata Version 9.2 (Stata, College Station, Texas); p values are 2-sided.

Results

Baseline clinical, angiographic, and procedural data. A total of 1,012 patients were randomly assigned to treatment with SES (503 patients with 694 lesions) and PES (509 patients with 715 lesions); 370 patients (37%) with 495 lesions had only small-vessel (RVD ≤2.75 mm), 504 patients (50%) with 613 lesions had only large-vessel (RVD >2.75 mm), and 138 patients (14%) with 301 lesions had small- and large-vessel (mixed) disease.

Baseline clinical and angiographic variables for all 3 groups are summarized in Tables 1 and 2. There were significant differences in the prevalence of hypertension ($p = 0.02$) and stable angina pectoris ($p = 0.01$). Among patients with acute coronary syndromes, ST-segment elevation myocardial infarctions were more frequent in those with stent implantations in large vessels only ($p = 0.002$). The incidence of multivessel disease was highest in the mixed-vessel disease group ($p < 0.001$). Target lesion involvement of the left anterior descending and circumflex coronary arteries was more frequent in the small-vessel group, whereas the right coronary artery was more frequently treated in the large-vessel population (Table 2). Lesion length and degree of stenosis were similar, whereas minimal lumen diameter and RVD differed among the 3 groups.

Procedural results are presented in Table 3. The number of lesions treated per patient was higher in the mixed group (2.2 ± 0.4), compared with small (1.4 ± 0.6) and large (1.2 ± 0.5; $p < 0.001$) vessels only. Stents implanted into large vessels were deployed at higher mean pressure than those implanted into small vessels ($p < 0.001$). With p values for interaction of ≥0.16, there was little evidence for

Table 5 Angiographic Follow-Up Results at 8 Months Stratified by Vessel Size

	Small Vessels Only				Large Vessels Only			
	SES	PES	Difference (95% CI)	p Value*	SES	PES	Difference (95% CI)	p Value*
Lesions (n)	134	136			159	143		
Minimal lumen diameter (mm ± SD)								
In-stent	2.29 ± 0.28	2.15 ± 0.55	0.15 (0.04 to 0.26)	0.01	2.75 ± 0.51	2.77 ± 0.61	−0.02 (−0.15 to 0.11)	0.76
In-segment	2.14 ± 0.39	1.94 ± 0.64	0.20 (0.07 to 0.34)	0.004	2.60 ± 0.58	2.66 ± 0.66	−0.06 (−0.20 to 0.08)	0.42
Stenosis (% of lumen diameter ± SD)								
In-stent	8.40 ± 8.36	14.46 ± 20.53	−6.06 (−9.97 to −2.14)	0.003	11.03 ± 14.26	13.06 ± 16.64	−2.02 (−5.71 to 1.66)	0.28
In-segment	13.36 ± 13.71	21.96 ± 24.27	−8.59 (−13.6 to −3.60)	0.001	15.31 ± 17.24	15.91 ± 18.00	−0.59 (−4.69 to 3.50)	0.78
Late loss (mm ± SD)								
In-stent	0.08 ± 0.18	0.26 ± 0.49	−0.18 (−0.28 to −0.09)	0.001	0.15 ± 0.44	0.23 ± 0.48	−0.08 (−0.19 to 0.03)	0.15
In-segment	0.12 ± 0.30	0.37 ± 0.60	−0.25 (−0.37 to −0.12)	0.001	0.23 ± 0.52	0.28 ± 0.52	−0.05 (−0.17 to 0.07)	0.41
Binary restenosis (%)								
In-stent	1.5	8.8	−7.3 (−13.3 to −1.3)	0.02	3.8	5.6	−1.8 (−6.6 to 2.9)	0.45
In-segment	4.5	16.2	−11.7 (−19.4 to −4.0)	0.003	7.6	7.0	0.6 (−5.3 to 6.4)	0.85

Values are mean ± standard deviation. *The p values relate to differences between patients treated with SES as opposed to PES for each stratum. The p values for interaction relate to differences in mean or percentage between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both small and large vessels.

Abbreviations as in Tables 1 and 4.

differences in procedural outcome between SES and PES in all 3 groups.

Clinical outcome. Clinical events at 2-year follow-up stratified for vessel size are listed in Table 4. In patients with small-vessel disease, SES more effectively reduced MACE than PES at 2 years (10.4% vs. 21.4%, respectively, hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.26 to 0.78; p = 0.004). This difference was largely driven by a 69% reduction in the risk of TLR in favor of SES (6.0% vs. 17.7%, HR 0.31, 95% CI 0.16 to 0.62; p = 0.001) (Fig. 1A). There were no significant differences between SES and PES in small-vessel disease patients with respect to death, cardiac death, or myocardial infarction at up to 2 years of follow-up.

Rates of MACE (10.4% vs. 13.1%, respectively, HR 0.78, 95% CI 0.46 to 1.29; p = 0.33) and TLR (6.9% vs. 8.6%, respectively, HR 0.79, 95% CI 0.42 to 1.49; p = 0.47) at 2 years were similar for SES and PES in patients with large-vessel disease (Fig. 1B). Similarly, there were no significant differences with respect to death, cardiac death, or myocardial infarction at up to 2 years of follow-up. In patients with both small- and large-vessel disease (mixed group), rates of MACE (16.7% vs. 18.0%, respectively, HR 0.91, 95% CI 0.41 to 2.05; p = 0.83) and TLR (16.7% vs. 15.4%, respectively, HR 1.08, 95% CI 0.47 to 2.50; p = 0.86) were comparable for SES and PES at 2 years (Fig. 1C). Differences between small- and large-vessel disease were driven by percutaneous TLR, and tests for interaction between treatment effect and vessel size reached formal statistical significance only for this outcome. When including additional terms for age, gender, diabetes, hypertension, and acute coronary syndrome for percutaneous TLR, we found the interaction between treatment and vessel size unaffected (data available on request).

The incidence of stent thrombosis was low and estimates of hazard ratios imprecise (Table 4). The cumulative frequency of stent thrombosis at 2 years amounted to 2.2% for SES and 2.7% for PES in small-vessel disease (HR 0.81, 95% CI 0.22 to 3.01; p = 0.75), 1.9% and 3.3%, respectively, in large-vessel disease (HR 0.58, 95% CI 0.19 to 1.78; p = 0.35), and 5.0% and 1.3%, respectively, in the mixed group (HR 3.93, 95% CI 0.41 to 37.8; p = 0.24).

Angiographic results. Angiographic follow-up at 8 months was obtained in 200 of 370 patients with small-vessel disease (54%), 252 of 504 patients with large-vessel disease (50%), and 68 of 138 patients with mixed disease (49%) (Table 5). Patients undergoing angiographic follow-up were younger (p < 0.001), less likely to have diabetes (p = 0.04) or hypertension (p = 0.04), and more likely to be male (p = 0.004) and to have experienced chest pain (p = 0.01). There was a difference in in-stent (2.29 ± 0.28 mm vs. 2.15 ± 0.55 mm; p = 0.01) and in-segment (2.14 ± 0.39 mm vs. 1.94 ± 0.64 mm; p = 0.004) minimal lumen diameter in favor of SES in small-vessel disease, whereas results were similar in large- and mixed-vessel disease. The SES more effectively reduced in-stent late luminal loss in all 3 subgroups, but differences were more pronounced in the small-vessel group (0.08 ± 0.18 mm vs. 0.26 ± 0.49 mm; p < 0.001). Although the rate of in-segment binary restenosis was significantly lower with SES (4.5%) than PES (16.2%; p = 0.003) in small-vessel disease, rates were similar in large-vessel (SES 7.6%, PES 7.0%; p = 0.85) and mixed-vessel disease (SES 9.1%, PES 12.8%; p = 0.55). Tests for interaction between treatment

Table 5 Continued

	Small and Large Vessels				
	SES	PES	Difference (95% CI)	p Value*	p Value for Interaction*
Lesions (n)	55	94			
Minimal lumen diameter (mm ± SD)					
In-stent	2.44 ± 0.58	2.37 ± 0.66	0.08 (−0.12 to 0.27)	0.43	0.17
In-segment	2.26 ± 0.65	2.18 ± 0.71	0.09 (−0.14 to 0.31)	0.44	0.03
Stenosis (% of lumen diameter ± SD)					
In-stent	12.76 ± 17.27	14.98 ± 20.27	−2.21 (−8.83 to 4.40)	0.51	0.29
In-segment	17.56 ± 20.28	21.18 ± 22.74	−3.62 (−11.61 to 4.38)	0.37	0.05
Late loss (mm ± SD)					
In-stent	0.15 ± 0.46	0.25 ± 0.52	−0.10 (−0.28 to 0.08)	0.26	0.35
In-segment	0.24 ± 0.51	0.33 ± 0.54	−0.09 (−0.29 to 0.11)	0.39	0.05
Binary restenosis (%)					
In-stent	5.5	8.5	−3.1 (−11.7 to 5.6)	0.49	0.23
In-segment	9.1	12.8	−3.7 (−15.6 to 8.2)	0.55	0.06

effect and vessel size reached formal statistical significance for in-segment minimal lumen diameter, diameter stenosis, late luminal loss, and binary stenosis.

Discussion

The principal findings of this subgroup analysis of the SIRTAX trial stratified by vessel size are as follows:

1. Sirolimus-eluting stents more effectively reduce rates of MACE and TLR in patients with small-vessel disease (RVD ≤2.75 mm).
2. The therapeutic benefit of SES over PES is maintained at 2 years' follow-up.
3. Differences in rates of MACE and TLR tend to be less pronounced in patients with large-vessel and mixed-vessel disease at 1 and 2 years' follow-up.
4. There are no significant differences between SES and PES with respect to death, cardiac death, myocardial infarction, or stent thrombosis in patients with small-, large-, and mixed-vessel disease at 2 years.
5. Sirolimus-eluting stents provide lower late luminal loss, translating into lower rates of binary restenosis, particularly in patients with small-vessel disease.

The results of the present study are biologically plausible, because a reduction in luminal diameter by a constant amount of neointimal hyperplasia results in a proportionally higher-grade diameter stenosis in small compared with large vessels. Moreover, SES have been invariably shown to afford lower late luminal loss in all trials with angiographic follow-up directly comparing SES and PES (13,14,18–20), and late luminal loss is an established marker to discriminate between different stent types (15). However, the impact of differences in late luminal loss on clinical outcome remains controversial, and the present study may help to identify patients who derive the greatest benefit from SES.

The findings of this subgroup analysis of a large-scale randomized trial directly comparing SES and PES are consistent with previously published data on: 1) indirect comparisons of SES and PES in small vessels (21–23); 2) registry experience comparing SES and PES in small vessels (24); and 3) direct comparison in a dedicated randomized trial of SES and PES in small vessels (25). Stone et al. (21) reported relatively high rates of restenosis (31%) and TLR (10.4%) in 108 patients treated with the 2.25-mm diameter PES in the TAXUS (In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation) V trial. In contrast, Nikolsky et al. (22) observed lower rates of restenosis (17%) and TLR (4.3%) in a similar patient population of 100 patients treated with 2.25-mm diameter SES. Similar results have been observed in the SES-SMART (Sirolimus-Eluting Stent and a Standard Stent in the Prevention of Restenosis in Small Coronary Arteries) trial (23) with restenosis and TLR rates of 10% and 7%, respectively, in SES-treated vessels. In a registry comparison of SES and PES from the Thoraxcenter, Rotterdam, rates of both TLR and MACE were higher for PES than SES (TLR: 5% vs. 1.4%; p = 0.08; MACE: 17.8% vs. 5.6%; p = 0.007) (24). In the REALITY (Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus]) trial (13), late loss was significantly lower in SES- compared with PES-treated patients, confirming the results of the present study. However, the difference in late loss in favor of SES failed to translate into a significant difference regarding binary restenosis (SES 9.6% vs. PES 11.1%; p = 0.31). This may be explained in part by a significantly lower postprocedural

in-stent minimal luminal diameter in SES compared with PES (2.08 vs. 2.16 mm; $p < 0.001$). Accordingly, the more potent effect of SES in reducing neointimal hyperplasia may have been offset in part by the inferior immediate postprocedural result.

Finally, a dedicated randomized trial directly compared SES and PES in a patient population of a size similar to the present subgroup analysis and observed significantly lower late loss (0.13 ± 0.56 mm vs. 0.34 ± 0.57 mm; $p < 0.001$), in-segment restenosis (11.4% vs. 19.0%; $p = 0.047$), and TLR (6.6% vs. 14.7%; $p = 0.008$) in SES- compared with PES-treated patients, respectively (25).

The impact of vessel size on outcome with DES has recently been evaluated by Elezi et al. (26). They observed lower late luminal loss for SES compared with PES in all 3 vessel size tertiles, which translated into a lower rate of TLR in favor of SES (8.6% vs. 16.4%; $p = 0.002$) only in the lowest vessel size tertile (RVD <2.41 mm). In a separate registry analysis of predictive factors of restenosis after implantation of SES and PES, Kastrati et al. (27) identified vessel size and DES type as strongest predictors of restenosis. Thus, results of a classification and regression tree revealed that rates of TLR were lower for SES than PES (7.8% vs. 15.6%) in vessels smaller than 2.6 mm and similar (7.2% vs. 7.2%) in larger vessels. The present study corroborates the findings of those studies and adds additional information, because the data were derived from a large-scale randomized trial with adequate concealment of allocation, minimizing the risk of selection bias at study entry (28) and assuring similar patient and lesion characteristics between SES- and PES-treated patients. Moreover, regular follow-up at predefined intervals provided additional rigor of data collection and allowed extending the observation period to 2 years.

The frequency of diabetes in the present study tends to be higher in small-vessel than in large-vessel disease, but is not as pronounced as reported by Elezi et al. (26), who described a higher frequency of diabetes in patients in the lowest vessel size tertile (RVD <2.41 mm). However, the frequency of diabetes in patients was similar in the middle tertile (RVD 2.41 to 2.84 mm). Differences in RVD between diabetic and nondiabetic patients in the TAXUS IV trial (29) and the SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) trial (30) were only minimal and in accordance with our results.

Study limitations. This is a subgroup analysis of a randomized trial not powered to detect treatment-subgroup interactions. It was not prespecified and is therefore exploratory in nature. A post hoc power analysis indicated that the trial would have a power of only 44% to detect a clinically relevant interaction between treatment and vessel size. Not surprisingly, the majority of interaction tests did not reach formal statistical significance and we cannot exclude that some of the observed differences in treatment effects between small- and large-vessel disease may have occurred by chance alone. However, the concordance between clinical and angiographic results suggests that the observed pattern may be real. Irrespective of the results of interaction tests, it can be concluded that SES is more beneficial than PES in small-vessel disease in terms of a reduction of TLR and MACE. The advantage of SES over PES appears less pronounced in large- and mixed-vessel disease, and interaction tests indicate that this trend toward a less pronounced advantage of SES over PES in large-vessel disease may have occurred by chance alone.

The SIRTAX trial was performed in an unselected "all comers" population, and 138 patients were treated for both small- and large-vessel disease (mixed group). These latter patients were more complex, as evidenced by a higher prevalence of multivessel disease and a nearly 2-fold higher number of lesions treated per patient compared with both the small- and the large-vessel disease groups. Although overall rates of MACE were similar for SES and PES in the mixed group, most of the adverse events were related to small vessels.

The rate of angiographic follow-up (51%) was low. This may have been related to the absence of a financial incentive and the broad inclusion criteria, with elderly patients and those with comorbid conditions being more reluctant to undergo repeat angiography than younger healthier patients typically included in angiography trials. Angiographic routine follow-up is known to increase the rate of TLR, and the incomplete angiographic follow-up in the present trial may have led to attrition bias (28), potentially resulting in an overestimation of differences in TLR and MACE between SES and PES. We consider this unlikely, because the difference in MACE in favor of SES was already apparent before the scheduled angiographic follow-up at 6 months (HR for MACE at 6 months 0.56, 95% CI 0.32 to 0.96; $p = 0.035$).

Conclusions

Vessel size remains an important determinant of adverse outcome in the DES era. Sirolimus-eluting stents are more effective than PES in reducing angiographic and clinical measures of restenosis. The benefit is particularly pronounced in small vessels less able to accommodate neointimal hyperplasia, whereas the selection of a particular DES appears less relevant in larger vessels. The observed therapeutic benefit is likely to apply to newer second-generation DES using limus analogues with similar reductions of late luminal loss but the potential for an improved safety profile.

Reprint requests and correspondence: Dr. Stephan Windecker, Professor and Head of Invasive Cardiology, Department of Cardiology, University Hospital, 3010 Bern, Switzerland. E-mail: stephan.windecker@insel.ch.

REFERENCES

1. O'Connor NJ, Morton JR, Birkmeyer JD, Olmstead EM, O'Connor GT, Northern New England Cardiovascular Disease Study Group. Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Circulation 1996;93:652–5.
2. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. Circulation 1998;98:1875–80.
3. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. Circulation 2005;111: 3435–42.
4. Meier B, Sousa E, Guagliumi G, et al. Sirolimus-eluting coronary stents in small vessels. Am Heart J 2006;151:1019el–7.
5. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
6. Park SW, Lee CW, Hong MK, et al. Randomized comparison of coronary stenting with optimal balloon angioplasty for treatment of lesions in small coronary arteries. Eur Heart J 2000;21:1785–9.
7. Kastrati A, Schomig A, Dirschinger J, et al. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. Circulation 2000; 102:2593–8.
8. Koning R, Eltchaninoff H, Commeau P, et al. Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. Circulation 2001;104:1604–8.
9. Agostoni P, Biondi-Zoccai GG, Gasparini GL, et al. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. Eur Heart J 2005;26:881–9.
10. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003;348:1537–45.
11. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
12. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
13. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs. paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial. JAMA 2006;295:895–904.
14. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
15. Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. Circulation 2005;112:2833–9.
16. Togni M, Windecker S, Wenaweser P, et al. Deleterious effect of coronary brachytherapy on vasomotor response to exercise. Circulation 2004;110:135–40.
17. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004;57:229–36.
18. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
19. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs. balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis. JAMA 2005;293:165–71.
20. de Lezo JS, Medina A, Pan M, et al. Drug-eluting stent for complex lesions: latest angiographic data from the randomized rapamycin versus paclitaxel CORPAL study. J Am Coll Cardiol 2005;45 Suppl A:75A.
21. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease. JAMA 2005;294:1215–23.
22. Nikolsky E, Moses JW, Cambier P, et al. Results from the 2.25 mm Sirolimus-Eluting BX Velocity Stent registry in patients with native coronary artery lesions. Am J Cardiol 2005;96 Suppl:179H.
23. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs. uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA 2004;292:2727–34.
24. Rodriguez-Granillo GA, Valgimigli M, Garcia-Garcia HM, et al. One-year clinical outcome after coronary stenting of very small vessels using 2.25 mm sirolimus- and paclitaxel-eluting stents. J Invasive Cardiol 2005;17:409–12.
25. Mehilli J, Dibra A, Kastrati A, Pache J, Dirschinger J, Schomig A. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. Eur Heart J 2006;27:260–6.
26. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. J Am Coll Cardiol 2006;48:1304–9.
27. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
28. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001;323:42–6.
29. Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. J Am Coll Cardiol 2005;45: 1172–9.
30. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS substudy. Circulation 2004;109:2273–8.